DECLARATION OF GILBERT R. GONZALES AND PAOLO L. MANFREDI UNDER 37 C.F.R § 1.132

1. We, Gilbert R. Gonzales and Paolo Manfredi, hereby state and declare the following:

2. I, Gilbert R. Gonzales, am a named inventor on the present application, U.S. Serial No. 10/669,490 ("the '490 Application"). I have B.Sc. (1973) and M.D. (1977) degrees from the University of Arizona. I have performed research in the area of pain, including methods for treating pain by use of methadone.

3. In addition to my research, I belong to the following scientific and medical societies: American Academy of Neurology (Facilitator, Physical Treatments of Chronic Pain, American Academy of Neurology Therapeutics and Technology and Assessment Subcommittee, May, 1992-1996; Member, American Academy of Neurology Continuum Committee on Pain, Kenneth Casey, Facilitator, March, 1994); American Pain Society; Eastern Pain Society; International Association for the Study of Pain; and the Western Pain Society.

4. I have also served on the following Editorial Boards: American Pain Society Journal, 1993 (ad hoc reviewer); Journal of Pain and Symptom Management, 1993-present (ad hoc reviewer); The Pain Medicine Journal Club Journal, 1994 (expert analyst); Pain Forum, 1999 (ad hoc reviewer); and The Clinical Journal of Pain, 2000 (ad hoc reviewer).

5. Additionally, I have held the following positions and appointments: Assistant Professor of Neurology, 1990-1992, Department of Neurology, University of Cincinnati School of Medicine, Cincinnati, Ohio; Assistant Professor of Neurology, 1992-1998 and Associate Professor of Neurology, 1998, Mayo Medical School; Vice

Chairman, Department of Neurology, 1994-1998, Mayo Clinic, Scottsdale, Arizona; Assistant Adjunct Professor, 1997-1998, Department of Psychology, University of New Orleans, New Orleans, Louisiana; Associate Attending Neurologist, 1998-2002, Memorial Hospital for Cancer and Allied Diseases, New York, New York; and Associate Member, 1998-2002, Memorial Sloan-Kettering Cancer Center, New York, New York.

6. I, Paolo L. Manfredi, am a named inventor on the '490 Application. I have an M.D. (1987) degree from the University of Genoa, Italy. I have postdoctoral training as a Pain Management Fellow at MD Anderson Cancer Center, Houston, Texas from July 1993 to June 1994, and at Massachusetts General Hospital, Boston, Massachusetts from July 1994 to June 1995. I have performed research in the area of pain, including methods for treating pain by use of methadone, and have authored numerous peer reviewed reports, book chapters, and other publications, a list of which is attached to this Declaration.

7. In addition to my research, I hold the following certifications from the American Board of Psychiatry and Neurology, Subspecialty Certification in Pain Medicine, (November, 2002), Certificate # 87; the American Board of Pain Medicine (February 1996), Certificate # 19796; and the American Board of Hospice and Palliative Care (October 2001), Certificate # 2004.

8. I have also served on the following committees: Cancer Care Committee, Lenox Hill Hospital (October 1995 - January 1997); and Pain Management Committee, Mount Sinai Medical Center (February 1997 - December 1998).

9. Additionally, I have held the following positions and appointments: Associate Fellowship Director (June 2003 - Present) and Fellowship Director

(December 1998 - June 2003), Pain and Palliative Care Service, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, New York 10021 (June 2003 - Present); Clinical Director, Palliative Care Program, and Director for Pain Management, Palliative Care Program, Department of Geriatrics, Mount Sinai Medical Center (February 1997 - December 1998); and Associate Clinical Director, New York Pain Treatment Program, Lenox Hill Hospital (October 1995 - January 1997); Consultant for Analgesic Studies, Jewish Home and Hospital, 120 West 106th Street, New York, New York 10025 (December 1998 - January 2000).

10. We have reviewed the references cited against the claims of the '490 Application: U.S. Patent Nos. 6,586,478 ("Ackman") and 6,264,981 ("Zhang"). In our opinion, one skilled in the art would not have looked to Ackman or Zhang to reach the presently claimed invention, nor would one skilled in the art combine the Ackman and Zhang references. In particular, neither Ackman, Zhang, nor their combination would cause one skilled in the art to conclude that methadone can be delivered transmucosally in a nonsedative composition for the treatment of patients with pain, particularly acute pain.

11. Ackman discloses a pharmaceutical composition for improving sleep. The composition of Ackman includes a nitric oxide mimetic and an established drug for sleep disorders. One skilled in the art would not look to Ackman for a nonsedative composition including methadone (as is disclosed and claimed by the '490 Application), due to Ackman explicitly describing a composition having sedative properties. As opposed to Ackman, when the composition including methadone of the '490 Application is used for pain treatment, sedation is reduced. Thus, a dosage form including

methadone for the treatment of sleep disorders (as described by Ackman) would not be a viable nonsedative treatment option, as is the presently claimed invention.

12. Further, Ackman lists several possible drugs as "established drugs for sleep disorders," including methadone (see at least at column 4, lines 21-32). In our view, the characterization of methadone as an established drug for sleep disorders is erroneous. To the contrary, methadone has never been approved for the treatment of sleep disorders. In our view, the disclosure of a methadone/nitric oxide-mimetic dosage form by Ackman, including the erroneous statement that methadone is a "well established drug for sleep disorders," would further steer one skilled in the art away from Ackman, because one skilled in the art would consider the overall teaching of Ackman to be fallacious.

13. Zhang discloses a transmucosal dosage form including opioid agonists such as fentanyl, alfentanil, sufentanil, lofentanil, and carfentanil. However, Zhang does not disclose methadone. In our opinion, methadone is not mentioned because Zhang did not, and others skilled in the art would not, contemplate that methadone could be useful for treating acute pain.

14. More specifically, the opioid agonists mentioned by Zhang have a very short half-life and are very short acting (measured in minutes to less than an hour), are very potent (and so are used in microgram amounts), and are pure mu opioid agonists (i.e., they bind to the mu opioid receptors and have no other known analgesic property). And, the drugs specifically disclosed by Zhang are synthetic opioids in the chemical structure group called anililidopiperidines. The characteristics of the drugs disclosed by Zhang are therefore very different and in some ways opposite from the

characteristics of methadone. Methadone is of a very different chemical structure group called diphenylpropylamines. Further, methadone has a very long half-life (up to several days) and has long-acting analgesic action, and it is much less potent (used in milligrams rather than micrograms). Due to these characteristics of methadone, people skilled in the art do not think, and would not think, that such a long-acting and less potent opioid can be used for acute pain. In other words, the use of methadone as a drug for acute pain is antithetical to the use of, and prevailing conventional wisdom regarding, methadone, as would be known to a person skilled in the art.

15. Further, methadone has unique pharmacodynamics well beyond opioid-like actions. For example, methadone is also an NMDA antagonist and a catecholamine re-uptake inhibitor, (both of these effects are analgesic), and therefore methadone is a unique drug that is not disclosed by mentioning the opioid family alone. Furthermore, as described above, the main mode of action of the drugs disclosed by Zhang is activation of the mu opioid receptor. These drugs do not work when the mu receptor is absent. To the contrary, methadone works very well as an analgesic in mice that are knockouts for the mu receptor gene, implying a different mode of analgesic action. In our opinion, it is therefore not surprising that Zhang did not disclose methadone because Zhang and others skilled in the art would not believe that methadone would work in treating and/or alleviating acute pain.

16. In summary, one skilled in the art would not consider a reference that teaches a sedative composition including methadone (Ackman) and a reference that specifically does not teach methadone for treating acute pain (Zhang) to reach the

presently claimed nonsedative composition that includes methadone for treating acute pain.

17. We hereby declare that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Further Declarants sayeth naught.

July 9, 2007
Date

Gilbert R. Gonzales

Date

Paolo L. Manfredi

presently claimed nonsedative composition that includes methadone for treating acute pain.

17. We hereby declare that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Further Declarants sayeth naught.

Date

Gilbert R. Gonzales

7/8/07
Date

Paolo L. Manfredi

Original Peer Reviewed Reports:

Kornick K, Kilborn M, Santiago-Palma J, Schulman,Thaler H, Keefe D, Katchman A, Pezzullo J, Ebert S, Woosley R, Payne R and Manfredi P. QTc interval prolongation associated with intravenous methadone. Pain 2003; 105: 499-506.

Panico K and Manfredi PL Institutional patterns of symptomatic medication in hospitalized patients with advanced cancer. Am J Hosp Pall Care. In press.

Manfredi PL and Houde RW. Prescribing Methadone, A Unique Analgesic. J Supp Oncology 2003. 1 (3): 216-219.

Manfredi PL, Breuer B, Wallenstein S, Stegmann M, Bottomley G and Libow L. Opioid Treatment for Agitation in Patients with Advanced Dementia. Int J Ger Psy 2003; 18:694-699.

Gonzales GR, Tuttle S, Thaler HT and Manfredi PL. Central Pain in Patients with Cancer. J Pain. 2003; 4 (6): 351-354.

Kornick C, Santiago-Palma J, Schulman G, O'Brien PC, Weigand S, Payne R and Manfredi PL. A Safe and Effective Method for Converting Patients from Transdermal to Intravenous Fentanyl for the Treatment of Acute Cancer-Related Pain. Cancer 2003; 97: 3121-4.

Manfredi PL, Foley KM, Payne R, Inturrisi CE and Houde R. Parenteral Methadone: an Essential Medication for the Treatment of Pain. J Pain Sympt Manage 2003; 26: 687-8

Manfredi PL, Gonzales GR, Ribeiro S, Chandler S, Payne R. Neuropathic pain in patients with cancer. J Pall Care 2003; 19 (2): 115-118.

Manfredi PL. Opioids versus antidepressants in postherpetic neuralgia: A randomized placebo-controlled trial. [Letter]. Neurology. Neurology. 2003 Mar 25;60(6):1052-3.

Panico K and Manfredi PL. Myocardial infarction associated with acute pain. J Pain Sympt Manag. 2003 Feb;25(2): 99-101.

Manfredi PL and Gonzales GR Symptomatic Uses of Caffeine in Patients with Cancer. J Pall Care 2003; 19 (1): 63-65.

Manfredi PL, Breuer BB, Meier DM and Libow L. Pain Assessment in Elderly Patients with Severe Dementia. J Pain Sympt Manag 2003; 25 (1): 48-52.

Katchman KN, McGroary KA, Kilborn MJ, Kornick CA, Manfredi PL, Woosley RL, and Ebert SN. Influence of Opioid Agonists on Cardiac HERG K+ Currents. JPET 2002; 303:688-694.

Moryl N, Santiago-Palma J, MD, Kornick C, Derby S, Fischberg D, Payne R and Manfredi P. Pitfalls of opioid rotation: substituting another opioid for methadone in the treatment of cancer pain. Pain 2002; 96 (3): 325-328.

Manfredi PL. CSF filtration for multiple sclerosis. [Letter]. Neurology 2002; 58 (6): 988.

Santiago-Palma J,Khojainova N, Kornick C, Fischberg DJ, Primavera LH, Payne R and Manfredi P. Intravenous methadone in the management of chronic cancer pain: safe and effective starting doses when substituting methadone for fentanyl. Cancer 2001; 92 (7):1919-1925.

Kornick C, Santiago-Palma J, Khojainova N, Payne R and Manfredi P. A safe and effective method of converting cancer patients from intravenous to transdermal fentanyl. Cancer 2001; 92(12):3056-61.

Manfredi PL, Gonzales GR and Payne R. Reversible spastic paraparesis induced by high dose methadone. J Pain. Feb 2001; 2 (1) 77-79.

Manfredi PL, Gonzales GR, Cheville AL, Kornick C and Payne R. Methadone analgesia in cancer pain patients on chronic methadone maintenance therapy. J Pain Sympt Manag. February 2001; 21(2):169-174.

Nelson JE, Meier DE, Oei EJ, Nierman DM, Senzel RS, Manfredi PL, Davis SM, Morrison RS. Self-reported symptom experience of critically ill cancer patients receiving intensive care. Critical Care Medicine. Feb 2001; 29(2):277-282.

Distasio SA, Salner AL, Brant JM, Fischberg D, Manfredi P. Brachial plexopathy after treatment for breast cancer. Cancer Pract. 2000 May-Jun;8(3):110-3.

Manfredi PL, Chandler SJ, Pigazzi A and Payne R. Outcome of cancer Pain Consultations. Cancer. Aug 2000: 920-924.

Manfredi PL, Morrison RS, Morris J et al. Palliative care consultations: how do they impact the care of hospitalized patients. J Pain Sympt Manag. Sept 2000; 20(3):166-173.

Manfredi PL, Shenoi S and Payne R. Sumatriptan for headache caused by head and neck cancer. Headache Oct 2000;40:758-760.

Pigazzi A and Manfredi PL. Under-treatment of pain: a risk associated with neuromuscular blockade in the intensive care unit. J Pain Sympt Manag. Feb 2000: 154-156.

Manfredi PL, Morrison RS, Meier DE. Opioids for pain and the rule of double effect.[Letter]. N Engl J Med 1998; 338: 1390.

Manfredi PL. Methadone for cancer pain. [Letter]. Pain 1998; 77:103-104.

Manfredi PL, Herskovitz S, Folli F, Pigazzi A, Swerdlow M,. Spinal epidural abscess: treatment options. Eur Neurol. 1998; 40:58-60.

Manfredi PL, Borsook D, Chandler SW, Payne R. Intravenous methadone for cancer pain unrelieved by morphine and hydromorphone. Pain 1997; 70: 99-101.

Manfredi PL, Chandler SW, Chou C, Patt RB, Payne R. High dose epidural infusion of opioids for cancer pain: cost issues. J Pain Sympt Manag 1997; 13: 118-121.

Manfredi PL, Ribeiro S, Chandler SW, Payne R. Inappropriate use of naloxone in cancer patients. J Pain and Sympt Manag 1996; 11: 131-133.

Book Chapters

Manfredi PL, Shreier G, Ling T. Cancer Pain. In Pappagallo M.,ed. The Neurologic Basis of Pain. McGraw-Hill. In Press.

Fischberg D, Manfredi PL, Meier DE. End of Life Care in the Hospital. In Watcher RM, Goldman L, Hollander H, eds. Hospital Medicine. Philadelphia: Williams & Wilkins. 2004. In Press.

Morrison RS, Carney MT and Manfredi PL. Pain Management. In: Rosenthal RA, Zenilman ME, Katlic MR, eds. Principles and Practice of Geriatric Surgery. New York: Springer; 2001:160-173.

Manfredi PL, Meier DE. End of Life Care in the Hospital. In Watcher RM, Goldman L, Hollander H, eds. Hospital Medicine. Philadelphia: Williams & Wilkins. 2000: 87-92.

Manfredi PL, Weinstein SM, Chandler SW, Payne R. Comprehensive medical management of cancer pain: opioid analgesia. In: WCV Parris, ed., Cancer pain Management: principles and practice. Butterworth - Heinemann. 1997; 48-64.

Patt RB, Manfredi PL. Cancer Pain Emergencies. In: WCV Parris (ed.), Cancer pain Management: principles and practice. Butterworth - Heinemann. 1997; 477-487.

Hacobian A, Stojanovic M, Tribble C, Manfredi P, Nishanian E. Emergencies in pain management. In: D Borsook, AA Lebel, B McPeek (eds), The Massachusetts General Hospital Handbook of Pain Management. Boston; Little, Brown and Company. 1996; 405-413.

Other Publications:

Manfredi PL. Methadone Injection Consensus group. AAHPM Bull. Winter 2004; 5 (1): 10-11.

National Pain Education Council. Monograph 3. www.npecweb.org. Management of Chronic Pain in Patients with Cancer or HIV/Aids. Contributing Editor. December 30, 2002. www.discovery-intl.com.

Gonzales GR, Manfredi PL, Payne R Tactile phi phenomenon in mononeuropathy patient with tactile allodynia The Journal of Pain, 2001. 1(2S1): 13.

Manfredi PL. Book Review. Pain and Suffering. By William K Livingston. Archives of Neurology 2000 57 (3): 246 .

Manfredi PL. The Simmonds' article reviewed. Oncology 1999; 13(8):1113-1114.

Manfredi PL, Ribeiro S. Physician's guide to pain management. Primary Care Sp. Ed. 1999; 3 (2) 59-62.

Manfredi PL, Patt RB. Book review: The medical care of terminally ill patients by R.E. Enck. Pain Digest 1994; 4:150.

Manfredi,P Morris J, Meier DE. Pain Management: Opioid Therapy Guidelines. Mount Sinai Medical Center 1998; Opioid Conversion Card for medical students and residents.